„BABEŞ-BOLYAI" UNIVERSITY
CLUJ-NAPOCA

Faculty of Chemistry and Chemical Engineering
Doctoral School of Chemistry

Topological characterization and functionalization of carbon nanostructures

PhD Thesis Summary

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CONTENTS

THESIS CONTENT

This present PhD thesis covers 135 pages and is grouped into three main chapters. The first part presents the definitions of chemistry from ancient times until today, the process of its development and its subordinate disciplines, one of which is nanotechnology, the research area of the thesis. Nanotechnology is presented as a collective term with examples of nanostructures such as carbon nanotubes, wich represent the main interest of my thesis.

The purpose of this thesis is the achievement of theoretical studies on carbon nanostructures, based on graph theory, to obtain advanced models for physicochemical and biological activity prediction as well as obtaining functionalized carbon structures used as support in the transport of different substances (drugs, enzymes, DNA, etc.) through cell membrane.

The introduction is followed by Chapter I, "Modeling molecular structures", focusing on QSAR / QSPR methods, with the purpose of finding connections between the molecular structure of substances and their properties in order to propose new molecular structures, yet unsynthesized, with potential biological activity. There are given general information about: encryption methods of physico-chemical and biological properties using matrices and topological indices; statistical elements; similarity of molecular structures and the used similarity software, Simil, etc. The last part discusses the personal contributions attributed to this chapter.

The next chapter discusses carbon nanostructures. There are presented various types of carbon nanostructures: fullerenes, graphene and carbon nanotubes. The classification, structure, symmetry and characterization of CNTs is followed by methods of construction, synthesis and functionalization of CNTs with various functional groups. There is also presented the applications of these promising structures in both chemistry and medicine. The last part of this chapter includes personal contribution given to this part of the thesis.

Chapter III discusses the capillarity of carbon nanotubes. In order to study their capillarity I used ammonium salts of heavy metals: Fe, Pb and Ni, following the amount of metal salt within the nanotube.

Keywords*: carbon nanotube, QSAR/QSPR, biological activity, functionalization, capillarity.*

I. MOLECULAR STRUCTURE MODELING

The projection of molecular structures with wanted physical-chemical or biological properties are one of the major desideratum's of molecular topology.

The identification of the crucial factors involved in the relation structure- property is gained by the comparative analyses of a set of molecules. This analysis is realized with the help of topological descriptors (indices), regression analysis included in various algorithms. The results of these analyses have diagnostic (ex. the utterance of a molecular property in an additive model throughout the contribution of structural fragments to global properties) or prognostic (ex. the estimation of molecular property from mathematical, physical, chemical or fragmentation properties) signification. The topological characterization of the chemical structures allows their classification based on similarity criterions.

Quantitative Structure – Property Relationship (QSPR) and Quantitative Structure – Activity Relationship (QSAR) studies give a simple and convenient (reasonable) support for predicting physical-chemical and biological properties. The bases of these methods are mathematical, chemical and environment studies. Based on molecular graphs and using structural descriptors are developed different mathematical models between molecular structures and physical-chemical or biological properties.

QSPR/QSAR looks for connections that link directly the molecular structure to the properties of the chemical compounds. By taking into consideration the structural information of a group of molecules with well known physical-chemical or biological properties from an experimental point of view and than manipulating these information is determined the mathematical relation for the prediction of the property. This method is inductive and it correlates structural characteristics with the value of the property. The error is minimal and it is verified and validated statistically.

The advantages of this method are: ►the reduction of biological tests, ►the reduction of costs and of time needed for synthesizing new compounds, ►optimalization of the resources granted for this industry, ►reduces the level of pollution, ►the synthesis of new active biological substances, etc.

I.1. Structure codification, information

A molecular graph can be represented by: a sequence of numbers, a polynomial, a single number or a matrix. These representations are aimed to be unique, for a given structure. Randić consideres that topological matrices can be accepted as a rational basis for designing topological indices, useful in correlational and similarity studies.

A number representing a chemical structure, in graph-theoretical terms, is called topological descriptor. Being a structural invariant, it does not depend on the numbering of the atoms or on the graphic representation of molecular graphs.

When a topological descriptor correlates with a molecular property it can be called molecular index or topological index (IT).

A topological index converts chemical structure into a numerical value, useful in QSPR / QSAR studies. Many topological indices have been proposed and their attempted correlations with different physicochemical properties (QSPR) or biological activities of the molecules (QSAR).

I.2. Elements of statistics

The design of molecular structures with desired physico-chemical or biological properties is the major target of the molecular topology. An insight of a set of molecules could reveal the crucial factors involved in the structure-property relationship.

This is performed by the aid of some molecular descriptors (e.g. topological indices) and/or the *regression analysis*, within various models (i.e. algorithms). The results of this analysis have a *diagnostic* meaning (e.g. the partitioning of a molecular property into fragmental contributions to a *computed* global property) and a *prognostic* one (e.g. the estimation of a molecular property from some fragmental mathematical or physico-chemical properties). The topological characterization of the chemical structures allows their classification according to some similarity criteria. The regression analysis is based on some basic *statistics*. Elementary statistical concepts providing the necessary foundations for more specific expertise in any area of statistical data analysis are briefly discussed in this chapter.

I.3. Regression models

Regardless of their type, two or more variables are related if in a sample of observations the values of those variables are distributed in a consistent manner. In other

words, variables are related if their values systematically correspond to each other for these observations.

The general purpose of *multiple regression* (the term was first used by Pearson[i], 1908) is to learn more about the relationship between several *independent* (or predictor) variables and a *dependent* (or criterion) variable.

In general, multiple regression allows the researcher to ask (and hopefully answer) the general question *what is the best predictor of ....*

The most frequently used multiple regression is *multiple linear regression* because this type of regression offers maximum capability in prediction. First of all, it is assumed that the *relationship between variables is linear*. In practice this assumption can virtually never be confirmed; fortunately, multiple regression procedures are not greatly affected by minor deviations from the linearity. However, it is prudent to always look at bivariate scatterplot of the variables of interest. If curvature in the relationships is evident, one may consider either transforming the variables, or explicitly allowing for nonlinear components.

Once this so-called *regression line* has been determined, the analyst can now easily construct a graph of the expected (predicted) values and the actual values of dependent variable. Thus, the researcher is able to determine which position is below the regression line, above the regression line, or at the regression line.

I.4. Advanced models in QSAR

A bioactive compound introduced into a living organism, induces a biological response (specific reaction) of the organism. The answer is conditioned by the structure and chemical identity of the bioactiv compound. The interaction of the bioactive compound with the living organism is happening at molecular level, in the so-called biological receptors. Such models are: the Hansch, Free-Wilson model, substructures analysis method DARC model Frel, etc.

I.5. Similarity

Similarity is one of the most common human abstractions . Because of its fundamental role in various situations and areas , the concept of similarity has attracted the interest of the scientific world. This attraction is reflected in numerous synonyms: equivalence, proximity, similarity, isomorphism, etc. The members of such a group will have one or more common attributes. Similarity is always considered in relation to a

particular characteristic of the group. If the similarity is well described mathematically, group members will satisfy an equivalence relation .

Current methods for measuring the similarity of two or more molecules, take into account the three different ways to describe a molecular structure: topological - using molecular graphs, based on the mathematical theory of graphs; configurational - by describing the atomic positioning in three-dimensional space with cateziene coordinates; quantum mechanic - using molecular field (eg electrostatic fields described as forms , with maximum and minimum) .

I.6. Personal contributions

Structure “design” in classes of benzodiazepine derivatives

Benzodiazepines caught the interest of scientists because of their putative role in mammalian central nervous system, which derives from their interaction with a macromolecular supercomplex involving their receptor and the $GABA_A$ receptor (a major inhibitory neurotransmitter). The action of GABA has been shown to be modulated upon the binding of various BZs. Because of this regulatory role and the exceptional tolerance to BZs even at high doses, they have become an important class of therapeutic agents with wide-spread applications in treatments related to anxiety and emotional disorders.

In this part of the thesis we used a set of 44 BZ derivatives, presented in the next table.

Table I.1. 1,4-benzodiazepine-2-ones derivates and binding affinity ($logIC_{50}$) values.

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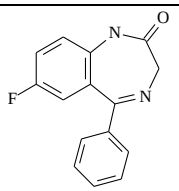
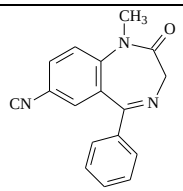
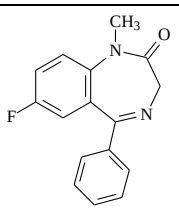
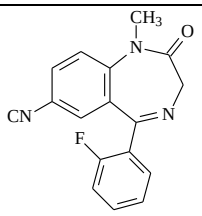
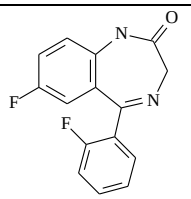
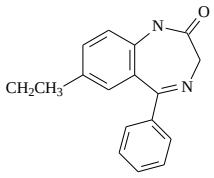
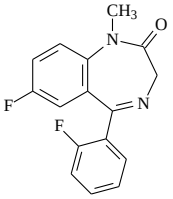
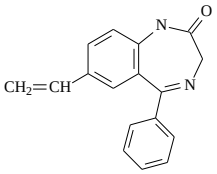
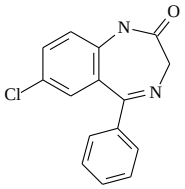
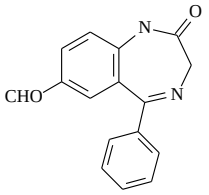
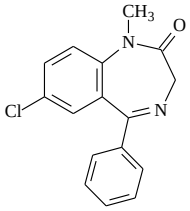
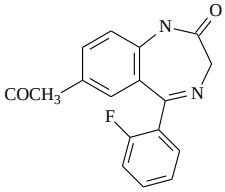
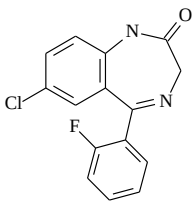
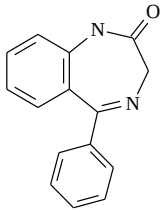
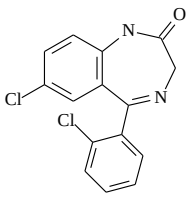
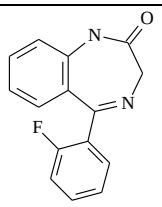
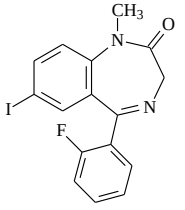
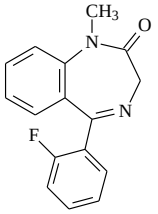
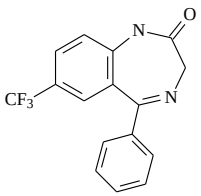
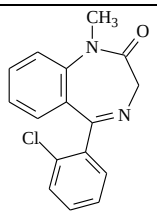
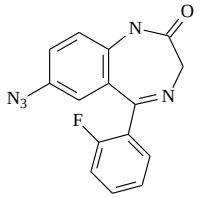
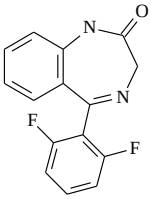
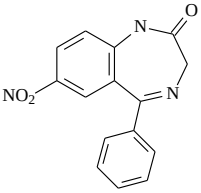
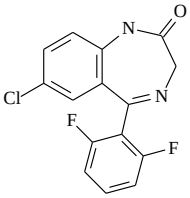
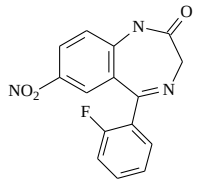
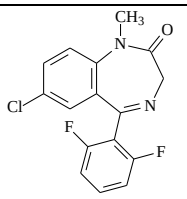
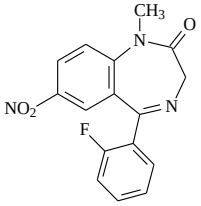
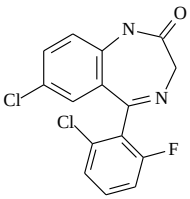
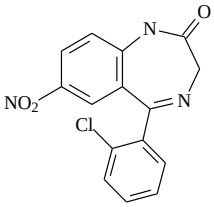
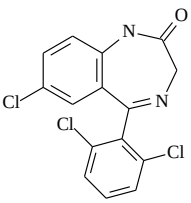
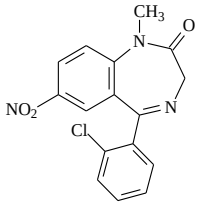
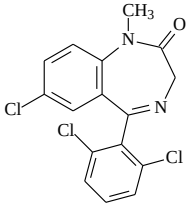
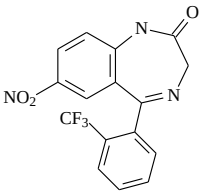
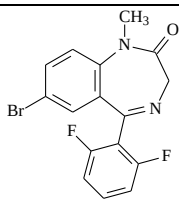
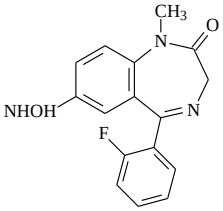
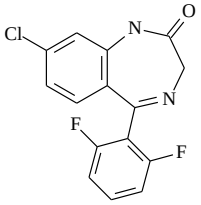
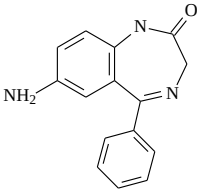
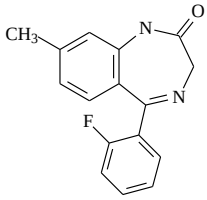
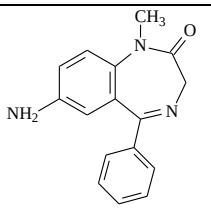
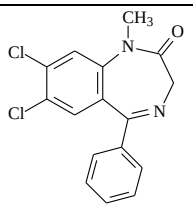
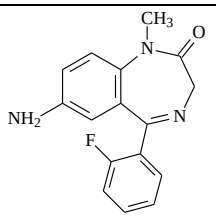
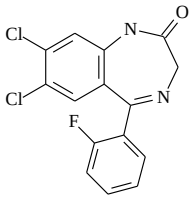
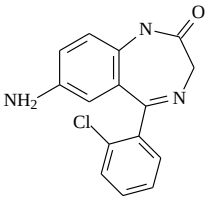
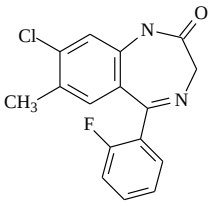
1		1.602	23		2.580
2		1.230	24		1.477

3		0.869	25		1.556
4		0.708	26		1.380
5		0.973	27		1.633
6		0.908	28		1.255
7		0.301	29		2.544
8		0.255	30		1.322
9		0.462	31		1.146

10		1.114	32		0.580
11		0.724	33		1.279
12		1.000	34		0.204
13		0.176	35		0.613
14		0.580	36		0.477
15		0.255	37		0.845
16		0.342	38		0.740

17		0.544	39		0.380
18		1.982	40		1.447
19		2.587	41		1.279
20		2.663	42		1.602
21		1.813	43		0.556
22		1.875	44		1.146

The following procedure was used to find the best relationship between structures and biological property:

1. the structures optimization to find a minimum-energy (stable) configuration (HYPER CHEM version 7.52),
2. generate the index database (DRAGON version 5.0),

3. searching for the best equation which has the correlation coefficient (R) higher than 0.90 (STATISTICA version 6.0),
4. graphical representation of the calculated versus observed biological property
5. the prediction of biological property for new structures

The best mono- and multivariate regression equations are:

Monovariate regression equation:

$$y= 13.61-0.83\times EEig04d \qquad (I.60)$$

R= 0.8264; s= 0.36; F= 47.38; n= 24

Bivariate regression equation:

$$y= 11.49-0.67\times EEig04d+0.281\times Hy \qquad (I.61)$$

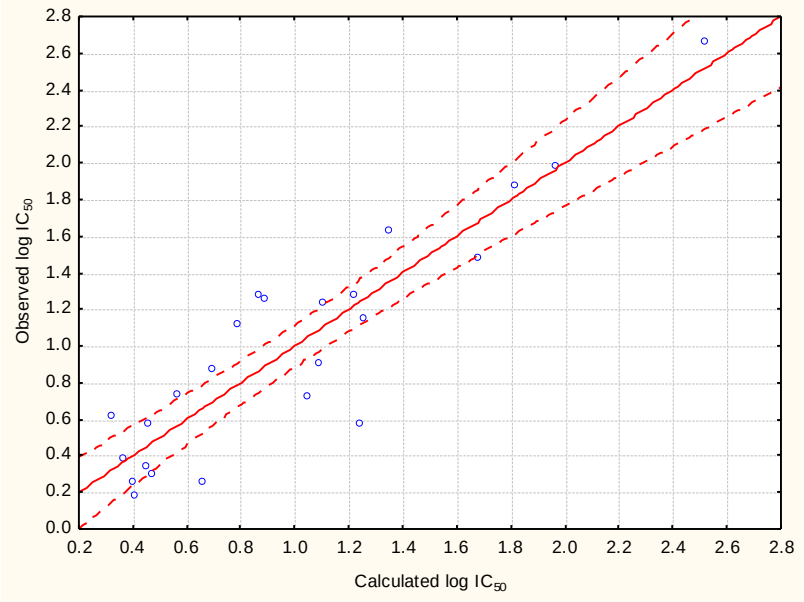
R= 0.8587; s= 0.34; F= 29.48; n= 24

Multivariate regression equation:

$$y= 12.32-1.79\times EEig04d+2.19\times Hy-3.03\times IC0-1.18\times nNH2 \qquad (I.62)$$

R= 0.9084; s= 0.29; F= 22.42; n= 24

The graphical representation, in accordance with the best regression equation (I.62), for the observed vs. calculated biological activity is shown in the following.

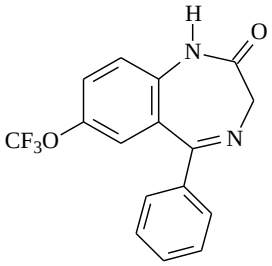
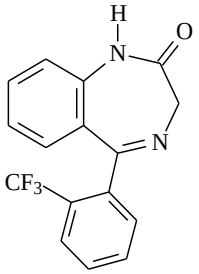
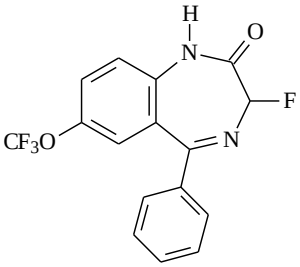
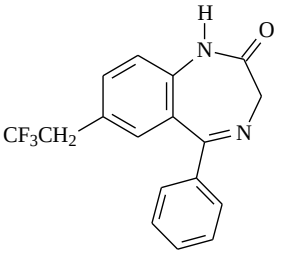
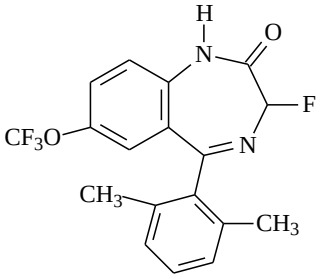
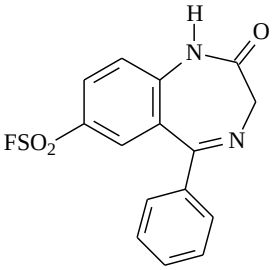
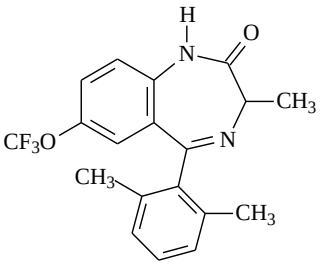
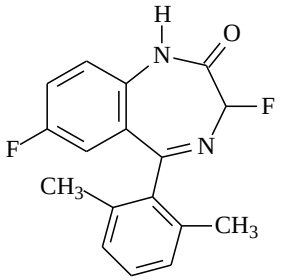


Graphic I.1. log IC_{50} calculated *vs.* observed for equation I.62

I.6.1.1. Design of new benzodiazepine derivatives

Based on the experimental data the structures which in position R_7 have the functional groups NO_2 or Cl show the highest biological activity. For this reason we tried to build up molecules with the same structure which don't have measured biological activity. The substituents for positions R_1 and R_2 were selected according to molecular similarity methods, and they are: H, CH_3, F, Cl. These molecules are presented in table I.5.

Table I.5. Constructed new structures

Nr.	Moleculă	Nr.	Moleculă
S1		S5	
S2		S6	
S3		S7	
S4		S8	

The next step was the calculation of the biological activity of the new structures. To calculate the biological property we used the best equation obtained by similarity method

(equation I.62). For this reason we calculated the descriptors used in this equation. The data are presented in table I.6.

Substituting the indices in equation I.62, we can calculate the biological activity for these new structures (table I.6).

Table I.6. Calculated indices and biological activity for proposed structures

Structuri	EEig04d	Hy	IC0	nNH_2	Activitate biologică
S1	2.73	-0.69	1.83	0	0.38
S2	2.79	-0.66	1.88	0	0.18
S3	2.87	-0.68	1.81	0	0.21
S4	2.86	-0.72	1.73	0	0.38
S5	2.62	-0.72	1.75	0	0.75
S6	2.70	-0.73	1.72	0	0.68
S7	2.58	-0.67	1.89	0	0.50
S8	2.61	-0.76	1.65	0	0.99

The table above shows that structures S2, S3, S1, and S4 show the highest values of biological activity. Of these structures, S2 shows the best value compared to the value of the structure in the initial set of molecules. Its biological activity (0.18) is very close to the value of the biological activityof the reference structure, SR (0,176). For this reason I think it would be interesting to synthesize this molecule and test its biological activity.

With Hyper Chem software we can calculate the log P: SR (-3.34); S2 (2.40); S3 (0.57). It is known that a positive value of log P indicates the hydrophobicity of the molecule, which is very useful and important in the transport of biologically active substances through biological membrane to the receptor. Summarizing this information our structure S2 seems promising in drug transport.

I.6.2. Modeling the biological activity of 2-aryl-thiazole derivatives

Using the same procedure as in the case of BZs derivatives, 14 molecular structures with antioxidant and antiinflammatory property were taken into consideration, from the class of 2-aryl-thiazole. The molecules and their properties are poresented in the following.

Table I.7. 2-aryl-thiazole derivatives and their properties

Molecule	Formula	IF	AF	NO	TOS	TAR
5b	$C_{31}H_{26}N_4O_3S_2$	16.57 ±1.51	22.86 ±3.02	577.49 ±96.07	33.54 ±2.97	1.0969 ±0.0026
5c	$C_{31}H_{23}F_3N_4O_3S_2$	22.57 ±2.76	45.71 ±4.23	595.8 ±38.61	31.04 ±3.78	1.097 ±0.004
7b	$C_{29}H_{23}BrN_4O_2S_2$	34.57 ±5.13	55.43 ±3.41	1183.35 ±134.13	27.62 ±2.03	1.0978 ±0.0022
7c	$C_{29}H_{20}BrF_3N_4O_2S_2$	23.43 ±3.95	32.28 ±4.07	1121.64 ±123.65	40.18 ±1.83	1.103 ±0.003
7e	$C_{29}H_{20}BrF_3N_4O_2S_2$	31.14 ±4.74	25.14 ±4.88	558.92 ±72.49	35.77 ±3.3	1.0963 ±0.006
7f	$C_{34}H_{24}BrN_3O_5S$	15.86 ±3.29	16.57 ±2.15	580.35 ±72.28	45.9 ±2.46	1.0979 ±0.0023
7h	$C_{29}H_{23}BrN_4O_2S_2$	29.43 ±4.12	58.71 ±2.21	1031.16 ±146.91	27.27 ±3.52	1.1018 ±0.0029
7i	$C_{29}H_{20}BrF_3N_4O_2S_2$	31 ±3.6	73.28 ±4.5	1228.8 ±120.04	25.92 ±2.64	1.104 ±0.0065
7k	$C_{29}H_{24}N_4O_2S_2$	28.57 ±2.99	42.28 ±4.23	1192.44 ±49.95	28.04 ±3.3	1.0983 ±0.0007
7l	$C_{29}H_{21}F_3N_4O_2S_2$	16.57 ±1.51	28.28 ±1.38	888.45 ±155.09	10.98 ±1.36	1.0882 ±0.002
7m	$C_{34}H_{25}N_3O_5S$	30.86 ±2.54	47.43 ±2.22	662.32 ±142.95	9.82 ±1.1	1.0855 ±0.0047
7o	$C_{29}H_{24}N_4O_2S_2$	27.43 ±5.09	62.28 ±4.53	1152.59 ±79.89	26.66 ±2.83	1.0989 ±0.0014
7p	$C_{29}H_{21}F_3N_4O_2S_2$	16 ±3.51	19.14 ±2.54	1257.04 ±157.09	22.57 ±3.44	1.0952 ±0.001
7r	$C_{34}H_{25}N_3O_5S$	26.28 ±4.82	15.43 ±0.79	1158.25 ±91.61	20.35 ±0.69	1.0992 ±0.0032

Modeling all five properties, the best obtained regression equations are:

In case of property IF:

Monovariate regression:

$$y = 27.02+0.849\times Mor13u \qquad (I.63)$$

$R = 0.8489$; $s = 1.14$; $F = 30.94$

Bivariate regression:

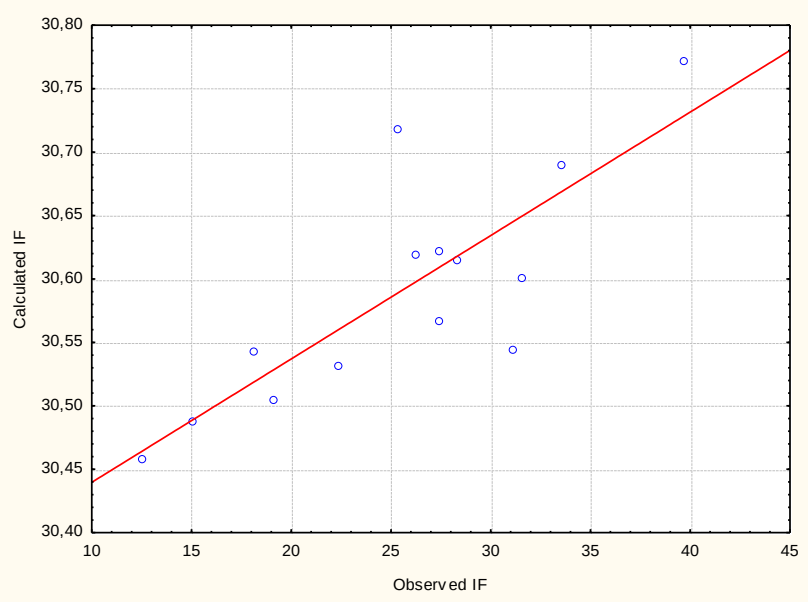
$$y = 21.70-0.31\times MATS3m+0.725\times Mor13u \qquad (I.64)$$

$R = 0.8958$; $s = 2.68$; $F = 22.35$

Trivariate regression:

$$y = 30.69-0.58\times MATS3m-1.7\times Mor13v+2.20\times Mor13p \qquad (I.65)$$

$R = 0.9481$; $s = 2.73$; $F = 29.64$



Graphic I.2. Calculated vs. observed IF according to eq. I.65

In case of property NO:

Monovariate regression:

$$y = 6564.2-0.89\times TIC2 \qquad (I.66)$$

$R = 0.8940$; $s = 139.58$; $F = 47.79$

Bivariate regression:

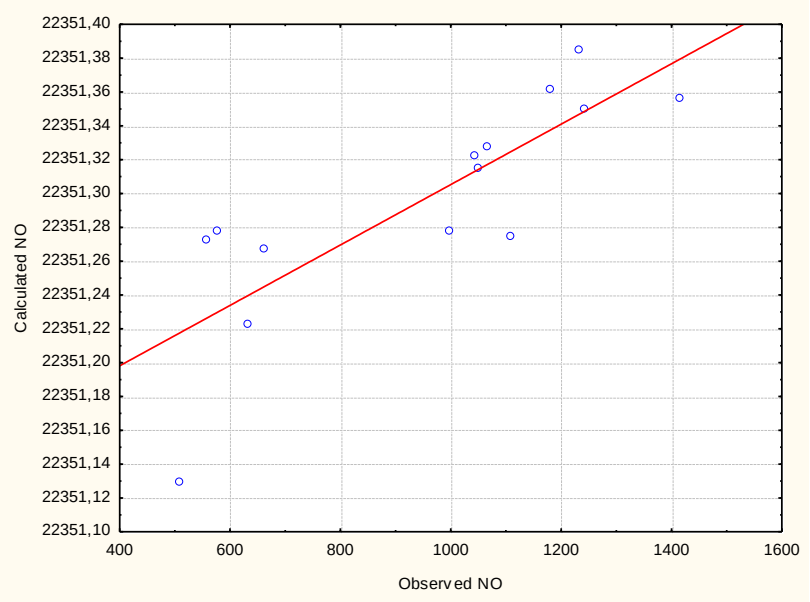
$$y = -9333.75-0.6\times IC3+0.475\times X[Sh[CfMax[Charge]]] \qquad (I.67)$$

$R = 0.9389$; $s = 112.03$; $F = 40.91$

Trivariate regression:

$$y = -22353.63+0.225\times ATS4p-0.68\times IC3+0.628\times X[Sh[CfMax[Charge]]] \qquad (I.68)$$

$R = 0.9427$; $s = 113.87$; $F = 26.61$



Graphic I.3. Calculated vs. observed NO according to eq. I.68

In case of property AF:

Monovariate regression:

$$y = -14.33+0.77\times R7p+ \qquad (I.69)$$

R = 0.7703; s = 12.25; F = 17.51

Bivariate regression:

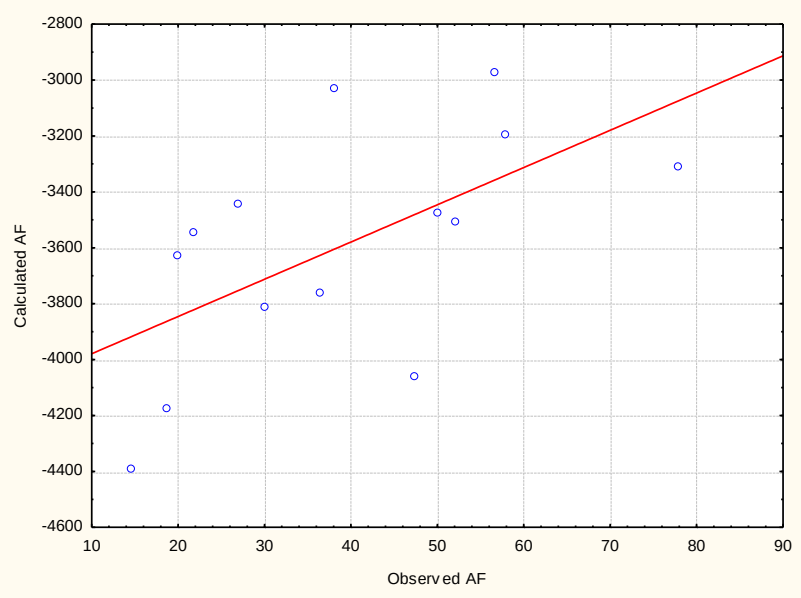
$$y = -4.31+0.658\times H2u-0.67\times PDS8[Sh[D3D]] \qquad (I.70)$$

R = 0.8829; s = 9.42; F = 19.44

Trivariate regression:

$$y = 101.94-0.55\times E3u-0.54\times PDS10[Sh[D3D]]+1.09\times R7p+ \qquad (I.71)$$

R = 0.9180; s = 8.35; F = 17.85



Graphic I.4. Calculated vs. observed AF according to eq. I.71

In case of property TOS:

Monovariate regression:

$$y = -333.6+0.87\times EEig10d \qquad (I.72)$$

R = 0.8702; s = 5.45; F = 37.44

Bivariate regression:

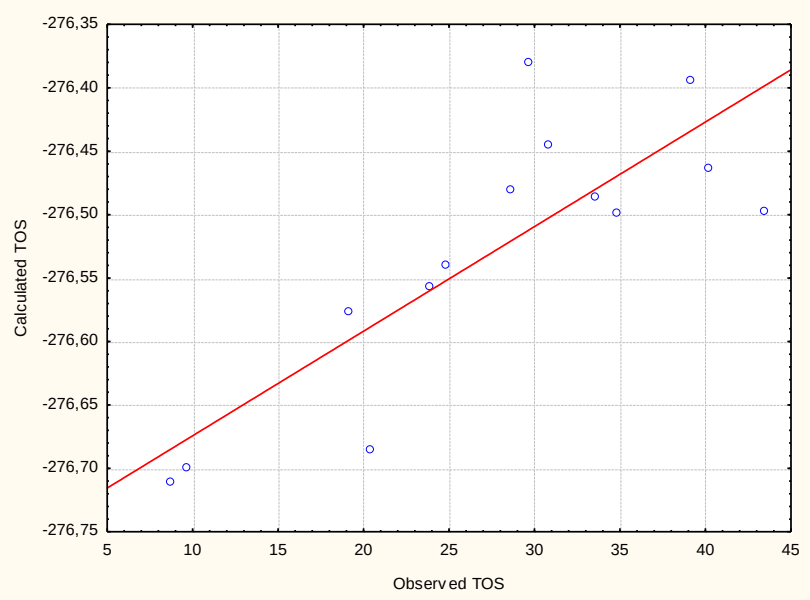
$$y = -278.28+0.741\times EEig10d-0.23\times Mor10v \qquad (I.73)$$

R = 0.8903; s = 5.26; F = 21.02

Trivariate regression:

$$y =134.52+0.15\times RDF040m-0.4\times RDF135u-0.35\times WkOp[SzMinSzMax\ U] \qquad (I.74)$$

R = 0.9473; s = 7.23; F = 6.03



Graphic I.5. Calculated vs. observed TOS according to eq. I.74

In case of property TAR:

Monovariate regression:

$$y = 1.22-0.88\times GATS2v \qquad (I.75)$$

R = 0.8818; s = 0.003; F = 41.93

Bivariate regression:

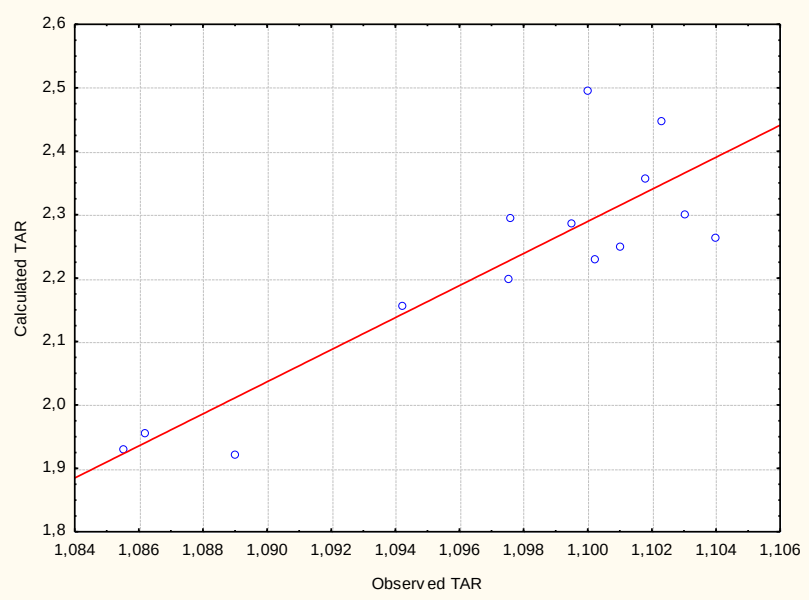
$$y = 0.96+0.562\times EEig10d-0.49\times Mor10v \qquad (I.76)$$

R = 0.9355; s = 0.002; F = 38.59

Trivariate regression:

$$y = 0.96+0.58\times EEig10d+0.566\times Mor10m-1.00\times Mor10v \qquad (I.77)$$

R = 0.9550; s = 0.002; F = 34.54



Graphic I.6. Calculated vs. observed TAR according to eq. I.77

Given that biological activity is a multi-conditioned response, our models have shown a clear correlation between the activity and the molecular structure, in particular bi- and trivariate equations. Considering this fact the present study should be continued by extending the data set, for a better statistical significance. Concluding, this theoretical study stands as support for future experiments in finding antioxidant and anti-inflammatory molecules with desired biological activities.

II. CARBON NANOSTRUCTURES

II.1. Fullerene

The main representative of the class is the icosahedral structured C60 fullerene, which is the smallest stable fullerene with non-adjacent pentagonal and hexagonal alternative faces. Icosahedron is a polyhedron composed of 12 pentagonal faces and 20 hexagonal faces, having a structure similar to a soccer ball.

II.2. Graphene

Grafena[98-103] is the two-dimensional version of graphite, with a planar arrangement of carbon atoms arranged in a hexagonal lattice.

II.3. Carbon nanotubes

Carbon nanotubes[104] (CNT) are carbon allotropes, first synthesized by Iijima in 1991. These cylindrical molecules exhibit properties that make them useful in a wide range of fields such as nanotechnology, electronics, optics and other fields of materials science.

II.4. Personal contribution

II.4.1. Nanoarchitectures by tetrapodal carbon nanotube junctions

Tetrapodal junctions are used to construct dodecahedral architectures (ex. diamond). They can be associated with the already synthesized spongy carbon, consisting only of sp^2 covalent carbon atoms, and the zeolites, periodic structures in the Euclidean space.

In this part of the thesis is discussed the structure and stability of two zigzag tatrapodal junctions (T_{j40} and T_{j52}). Series of objects are built up by connecting a various number of junctions. Geometry optimization and single point computations (total energy E_{tot} and HOMO-LUMO gap energy E_{gap}) were performed at the Hartree–Fock level of theory in view of evaluating their stability.

Figure 1. Tetrapodal open units: T_{j40} (left) and T_{j52} (right)

Data obtained using HF/6-31G(d,p) method are listed in Table 1 while the data computed by HF/3-21G* are listed in Table 2. The strain energy, evaluated according to POAV theory of Haddon[27,28] is also included in these tables. One can see that the closed fullerenes (Table 1, entries 1, 4 and 6) show a higher strain in comparison to the open structures, the lowest value being for the IPR fullerene C_{60}, the reference structure in nanoscience. Observe the higher symmetry of the charged T_{j40}^{-4} resulted in higher strain, when compared with the neutral lower symmetry T_{j40}. Even the presence of hydrogen atoms on the open structures prohibits a direct comparison with the close fullerenes, data in Table 1 suggest the stability of the tetrapodal structure stability is close to that of C_{60}.

The strain decreases in structures with more than one repeating unit (see Table 2) while the HOMO-LUMO gap increases for the (hyper) cycles (Table 2, entries 3 and 6), with T_{j40}-hexagon being the most stable structure in this table.

Table II.3. Energetic data of tetrapodal junctions and their spanned fullerenes using HF/6-31G(d,p).

	Structures	E_{tot} (eV) / C atom	E_{gap} (eV)	Strain Energy (kcal/mol)	Symmetry
1	C_{44}	-37.852	6.595	12.73	*T*
2	T_{j40}	-38.021	6.681	5.80	D_2
3	T_{j40}^{-4}	-38.006	7.414	6.70	*T*
4	C_{56}	-37.854	5.505	10.65	T_d
5	T_{j52}	-37.986	6.144	5.44	D_{2d}
6	C_{60}	-37.864	7.418	8.256	I_h

Table II.4. Energetic data of tetrapodal junctions using HF/3-21G*.

	Structures	E_{tot} (eV) / C atom	E_{gap} (eV)	Strain Energy (kcal/mol)	Symmetry
1	T_{j40}-dimer	-37.768	1.698	5.31	C_3
2	T_{j40}-trimer	-37.755	0.927	5.03	C_2
3	T_{j40}-hexagon	-37.728	7.382	4.57	D_3
4	T_{j52}-dimer	-37.741	1.247	4.90	D_{3h}
5	T_{j52}-trimer	-37.731	0.891	4.67	C_{2v}
6	T_{j52}-pentagon	-37.711	6.755	4.25	D_{5h}

II.4.2. Modeling carbon nanotubes

One of the biggest concerns of molecular topology is the projection and synthesis of molecular structures with desired, specific physico-chemical or biological properties in order to enlarge their applicability.

In this part the objective of the thesis is the modeling of carbon nanotubes and their functionalization with diamine derivatives with potential use in medicine, where they can serve as raw material for the binding reactions of therapeutic agents to nanotubes.

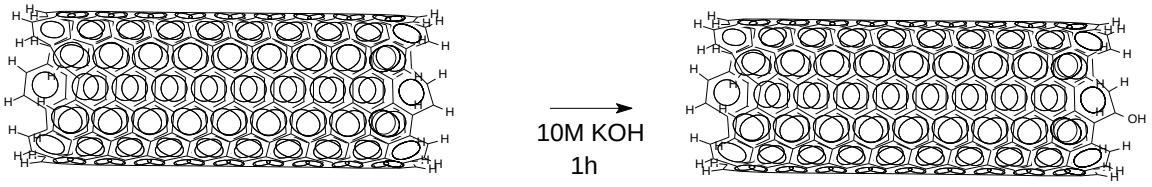
By the aid of NANOSTUDIO software, developed in our group, carbon nanotubes of different length CNT (n,m,u) were generated, where n and m, are the number of unit vectors along the two directions on the hexagonal crystal structure of graphene and u-is the length of the nanotube. Throughout HYPER CHEM software the functionalization of CNT was carried out with -OH, -COOH and -NH_2 functional groups and the theoretical study of their stability.

From the results it is apparent that functionalization of the nanotubes at one of the ends, leads to an increase of energy and therefore to an increase in their ability to react with different chemical compounds. Also, the longer the nanotubes are, there can be observed an increase in their reactivity.

From energy calculations we can observe an increase in stability with the driftment of functional group towards positions inside of the nanotube, which can be also deducted from the fact that structural defects in the formation of nanotubes always appear at the end of the structure. Taken this fact into consideration, further reactions will have as starting structures functionalised CNTs at one of the ends, because the carbon atom from this position has lower energy, therefor it is more sensitive towards chemical reactions.

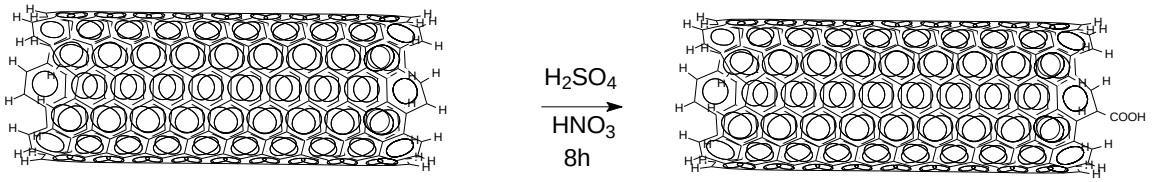
II.4.3. Functionalization of CNT with –OH and –COOH groups

In order to obtain the –OH functionalized product[168] SWCNT, DWCNT and MWCNT (*Chengdu Organic Chemicals Co. Ltd., Chinese Academy of Sciences*) were suspended in a solution of potassium hydroxide (50 mL, 10M KOH, Mw = 56.1056 g/mol, ρ=2.044 g/cm^3) for one hour in an ultrasonic bath (Transsonic 460/H, ELMA AUSTRIA, 100W, 40kHz). The resulted suspension was heated at 100 ° C for an additional hour, filtered under vacuum through membrane (PTFE, 0.2 μm porosity diameter), washed in double distilled water (3x15 mL) and allowed to dry in the oven. The hydroxylated product is characterized by FT-IR spectroscopy (FT-IR BRUKER EQUINOX 55, 7500-370cm^{-1}, resolution > 0.5cm^{-1}, Michelson type interferometer and DLATGS detector).



Scheme II.3. Schematic representation of the hydroxylation of CNTs

The oxidation of carbon nanotubes according to literature[168] is carried out by suspending carbon nanotubes (20 mg, Chengdu Organic Chemicals Co.. Ltd., Chinese Academy of Sciences) in a mixture (20 ml, (1:3)) of sulfuric acid (H_2SO_4, 98%, Mw=98.08g/mol, ρ=1.84g/cm^3) and nitric acid (HNO_3, 70%, Mw=63.01g/mol, ρ=1.3913g/cm^3) for 8 hours in an ultrasonic water bath (TRANSSONIC 460/H, ELMA AUSTRIA, 100W, 40kHz). The resulting solution was centrifuged to remove the unreacted acid mixture. The product thus obtained is left to dry under vacuum and is characterized by FT-IR spectoscopy (FT-IR BRUKER EQUINOX 55, 7500-370cm^{-1}, resolution> 0.5cm^{-1}, Michelson-type interferometer, DLATGS detector).



Scheme II.3. Schematic representation of the oxidation of CNTs

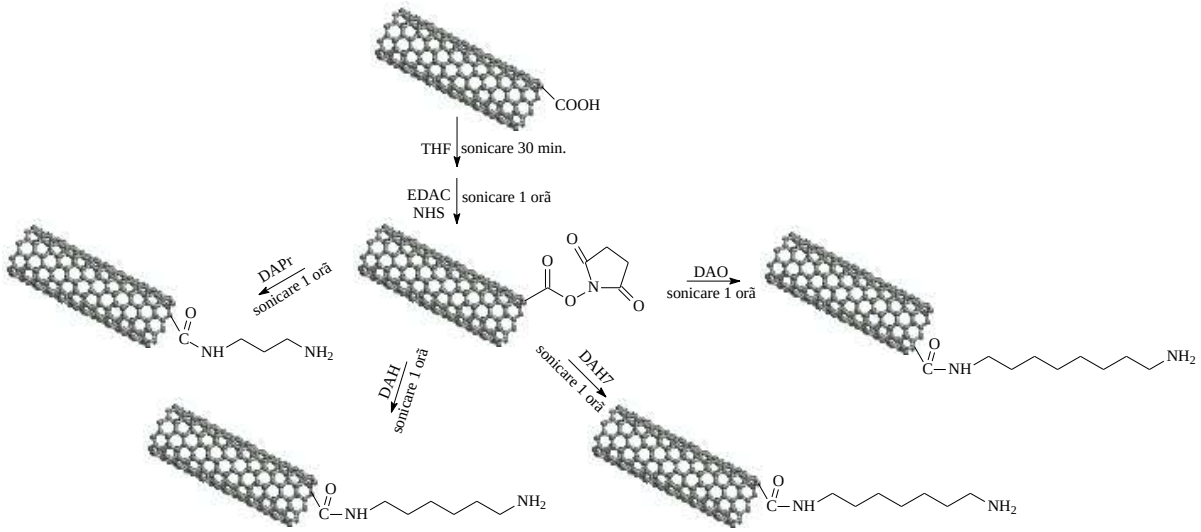
II.4.4. Functionalization of CNT with diamine derivatives

To obtain functionalized CNT with diamines the following method of synthesis has been used. 10 mg of SWCNT-COOH, DWCNT-COOH and MWCNT-COOH were suspended in tetrahydrofuran (15 mL, THF, C_4H_8O, Mw=72.11g/mol, ρ=0.8892g/cm^3) in a 25 mL flask and placed into ultrasonic water bath (Transsonic 460/H, ELMA AUSTRIA, 100W, 40kHz) for 30 minutes, at room temperature.

Afterwords 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (10 mg, EDAC, $C_8H_{17}N_3Cl$, Mw=191.7g/mol) and N-hydroxy-succinimide (6 mg, NHS, $C_4H_5NO_3$, MW=115.09g/mol) was added and the mixture was sonicated for one hour, at room temperature.

Finally the diamino-alkanes were added to the mixture (1,3-diaminopropane: 10µl, 1,6-diaminohexane: 15.15mg, 1,7-diaminoheptane: 17mg, respectively 1,8-diaminooctane:

18.81mg) and sonicated for one hour. The resulting products were filtered under vacuum on PTFE membrane, washed with THF (3×15mL) and dried.



Scheme II.6. Schematic representation of the functionalization of CNTs with diamines: DAPr, DAH, DAH7 respectively DAO

II.4.5. Elemental analysis of simple and functionalized CNT

The results are summarized in the following table for each product.

Table II.24. Elemental analysis results

Analysed nanostructure	Measured quantity (mg)	N (%)	C(%)	H(%)
SWNT	1	0.07265	99.1445	0.95755
DWNT	1.1	0.03774	97.8194	0.74945
MWNT	1.2	0.00577	90.4331	0.74667
S-COOH	1.04	0.02661	91.1995	1.10909
D-COOH	0.88	0.03145	85.3826	1.55408
M-COOH	1	0.02768	88.9994	1.43888
S-DAPr	0.94	10.1645	53.095	6.59545
S-DAH	1.01	10.59204	64.74846	8.331705
S-DAH7	1.06	7.68883	59.82219	6.26393
S-DAO	1.01	7.139163	57.68488	5.834258
D-DAPr	1	8.749095	55.19902	5.466196
D-DAH	1	7.980703	63.43407	5.709854
D-DAH7	1.02	7.888126	64.37891	6.44537
D-DAO	0.99	8.206158	65.17282	6.531731
M-DAPr	1.03	8.532155	48.67519	5.766283
M-DAH	1.04	8.08721	56.29444	5.842718
M-DAH7	0.99	6.893759	50.82919	5.814746
M-DAO	1.03	6.806996	52.25743	5.607614

Mass percentages of unfunctionalized and functionalized nanostructures reported to 1mg substance are shown in table II.25.

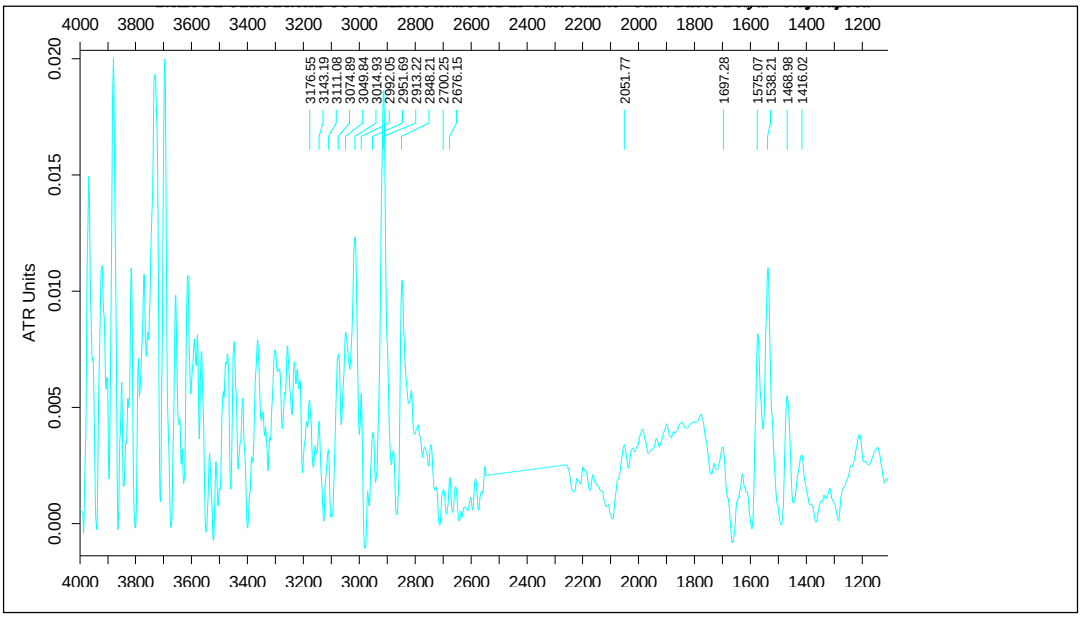
Table II.25. Mass percentages of the analysed structures

Analysed nanostructure	Mass percentage		
	N (%)	C(%)	H(%)
SWNT	0.07265	99.1445	0.95755
DWNT	0.034309	88.92673	0.681318
MWNT	0.004808	75.36092	0.622225
S-COOH	0.025587	87.69183	1.066433
D-COOH	0.035739	97.02568	1.766
M-COOH	0.02768	88.9994	1.43888
S-DAPr	10.8133	56.48404	7.016436
S-DAH	10.48717	64.10739	8.249213
S-DAH7	7.253613	56.43603	5.909368
S-DAO	7.068478	57.11374	5.776493
D-DAPr	8.749095	55.19902	5.466196
D-DAH	7.980703	63.43407	5.709854
D-DAH7	7.733457	63.11658	6.31899
D-DAO	8.289048	65.83113	6.597708
M-DAPr	8.283646	47.25747	5.598333
M-DAH	7.776163	54.12927	5.617998
M-DAH7	6.963393	51.34262	5.873481
M-DAO	6.608734	50.73537	5.444285

From the data obtained one can see that in each case the chemical reaction was achieved, obtaining the desired functionalized nanotubes. The reaction rate decreases with the increasing of the length of the carbon chain. Thus, 1,3-diaminopropane has a greater reaction rate than 1.8-diaminooctane, which can be explained on base of sterical effects which makes it harder to get close to the reaction center.

II.4.6. FT-IR analysis of simple and functionalized CNT

In all cases FT-IR analysis showed different bond types at their specific wavelenght, which proves that reactions took place and the functionalized products were obtained. For example the spectrum for MWCT-DAPr is presented in the next graphic. The peak for C=O is around 1685 cm^{-1} wavelenght; for N-H at 3176 cm^{-1}; C-N at 1202 cm^{-1}.



Graphic II.15. IR spectrum for MWCNT-DAPr

II.4.7. TEM characterization of CNT

TEM characterization also showed that the desired poducts were obtained. In the next figures are presented a few TEM images for some of the obtained products.

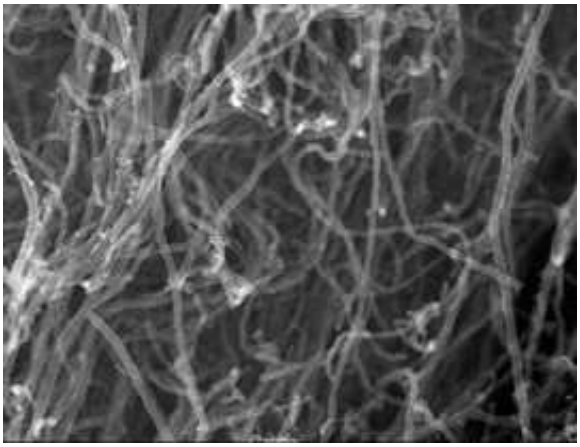


Figure II.24. Simple MWCNT

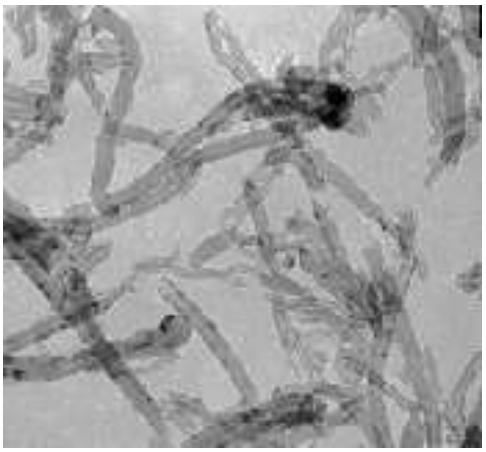


Figure II.27. MWCNT-OH

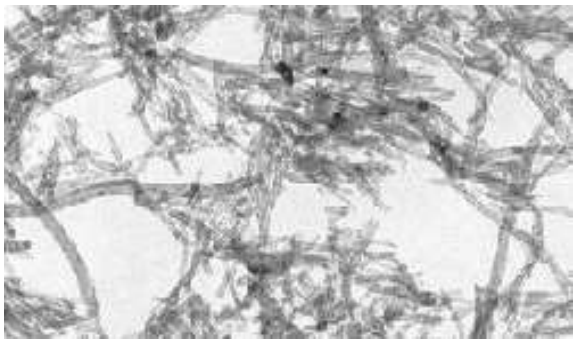


Figure II.30. MWCNT-COOH

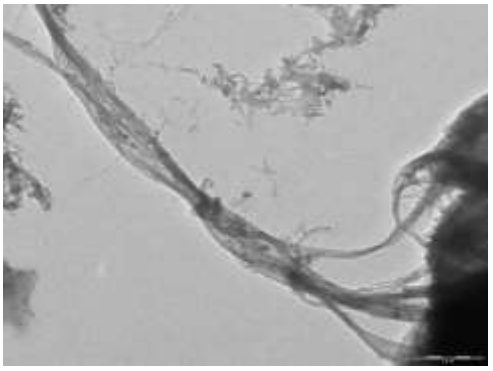


Figure. II.39. MWCNT-DAPr

III. CAPILLARITY OF CARBON NANOTUBES

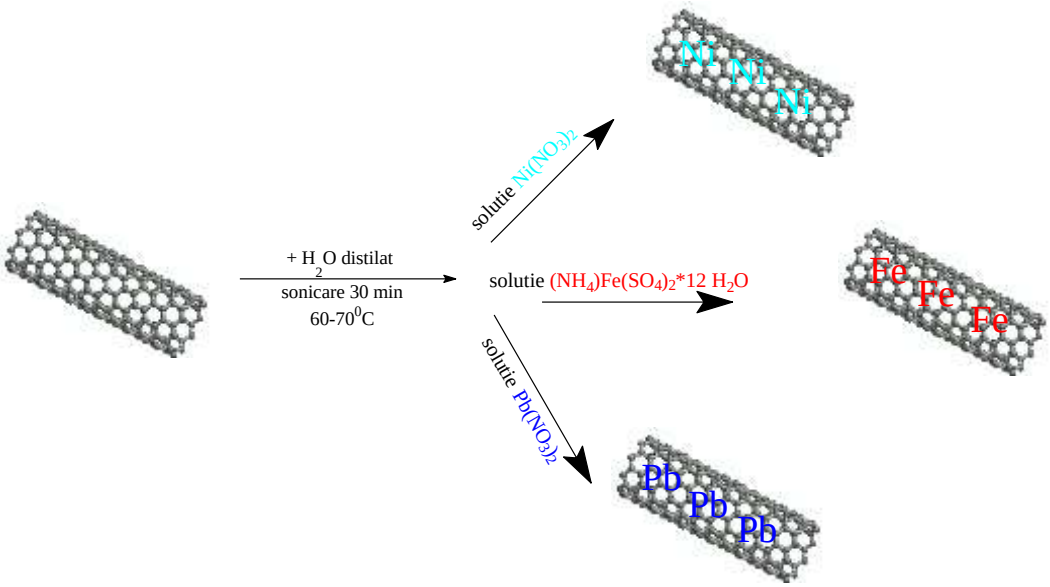
Carbon nanotube capillarity[173] is directly related to the surface energy of the liquid-solid surface of the nanotube interaction, thus it is a wetting problem. This is supported by the Young-Laplace equation, which connects the liquid-vapor pressure difference **ΔP** to the surface tension of the liquid γ and solid-liquid contact angle θ, by the following:

$$\Delta P = 2\gamma\cos\theta r^{-1}$$

where **r** is the curvature radius of the meniscus.

III.1. Personal contributions

10 mg of SWCNT, DWCNT and MWCNT (Chengdu Organic Chemicals Co.. Ltd., Chinese Academy of Sciences) were suspended in 10 ml distilled water and sonicated (Transsonic 460/H, ELMA AUSTRIA, 100W, 40kHz) at 60-70°C for 30 minutes. To the suspension is added 10 ml, 2 M, double sulphate of ammonium iron, lead nitrate and nickel nitrate solution, at room temperature on a magnetic stirrer and stirred for 12 hours. Subsequently it was washed with distilled water, filtered on filter paper and placed in a vacuum oven to dry. The end products are carbon nanotubes (single wall, double wall and multiple) filled with the above mentioned metal salts and are characterized by FT-IR spectroscopy, elemental analysis and TEM microscopy.



Scheme III.1. Schematic representation of CNT capillarity with metal (Ni, Fe, Pb) salts

The results from elemental analysis are presented in the next two tables.

Table III.1. Elemental analysis results

Analysed nanostructure	Measured quantity (mg)	N (%)	C(%)	H(%)
SWCNT-FE	1.17	0.91364	25.7852	1.63961
DWCNT-FE	1.07	1.06369	42.7234	1.95992
MWCNT-FE	1.05	1.4892	22.4771	2.37743
SWCNT-PB	1.06	0.365524	88.6937	0.861491
DWCNT-PB	1	0.224863	93.46508	0.764207
MWCNT-PB	0.99	0.775751	82.45634	0.95855
SWCNT-NI	1.07	0.229551	84.59657	0.940371
DWCNT-NI	1.13	0.146949	90.90116	0.796721
MWCNT-NI	0.99	0.146764	84.13317	0.981677

Tabel III.2. Mass percentage of the analysed structures

Analysed nanostructure	Mass percentage		
	N (%)	C(%)	H(%)
SWCNT-FE	0.780889	22.03863	1.401372
DWCNT-FE	0.994103	39.9284	1.831705
MWCNT-FE	1.418286	21.40677	2.264215
SWCNT-PB	0.344834	83.6733	0.812727
DWCNT-PB	0.224863	93.46508	0.764207
MWCNT-PB	0.783587	83.28923	0.968232
SWCNT-NI	0.214534	79.06221	0.878852
DWCNT-NI	0.130043	80.44351	0.705063
MWCNT-NI	0.148246	84.983	0.991593

One can see that the best capacity of capillary can be attributed to MWCTs, because of their large internal diameter, and from the salts Fe shows the best capacity to enter into the cavity of CNTs, due to its smaller size.

In the following there are presented TEM images of some of the obtained products.

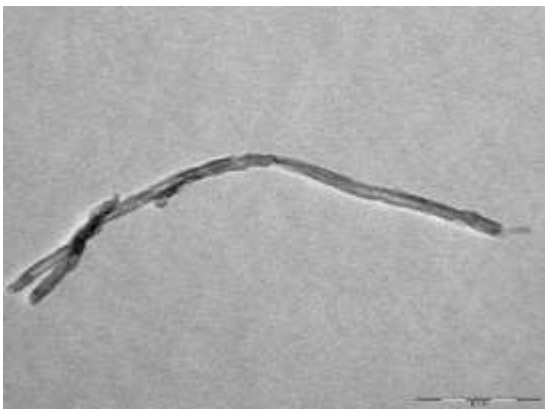


Figure III.7. MWCNT-Ni

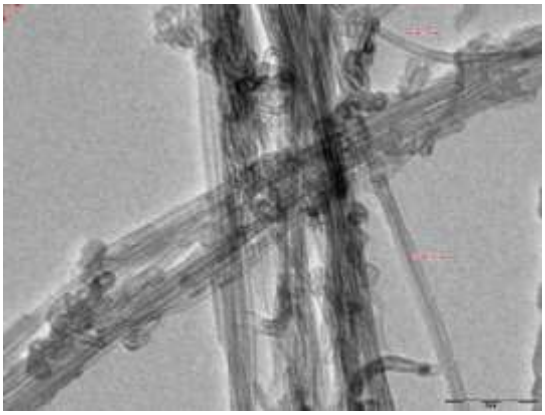


Figure III.8. MWCNT-Pb

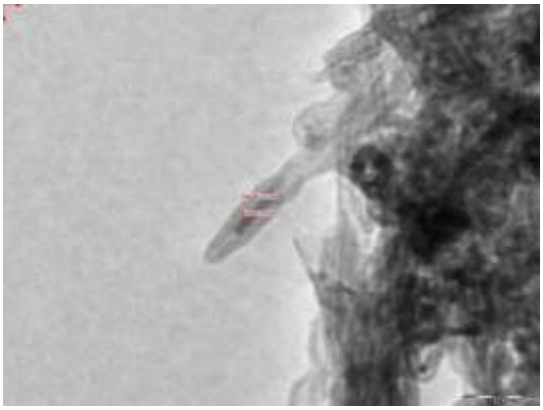


Figure III.9. MWCNT-Fe

GENERAL CONCLUSIONS

The overall aim of the thesis is the development of theoretical studies on carbon nanostructures, based on graph theory, to achieve advanced models for predicting physicochemical and biological activities, as well as obtaining functionalized carbon structures, used as support in the transport of different substances (drugs, enzymes, DNA, etc.) through cell membrane.

Conclusions and personal contributions resulting from the entire research demonstrates that the overall objective of the doctoral thesis was achieved throughout the following specific objectives:

- ✓ Chapter I – By similarity search in two different classes of biologically active compounds (benzodiazepine and 2-aryl-thiazole derivatives) I proposed new, yet unsynthesized, structures with a calculated biological activity very close to that of the reference structure (RS).
- ✓ Chapter II - CNT modeling and theoretical study of their stability with the purpose of their functionalization, having possible application in medicine as carriers of biologically active vectors to the target cells through cell membrane.
- ✓ Chapter III - The study of CNT capillarity with different salts of heavy metals: Ni, Fe, respectively Pb.

Focusing on QSAR/QSPR studies, based on graph theory, in the personal contributions presented in chapter I, structures were optimized to find the most stable configuration (HYPER CHEM version 7.52), an index database was generated (DRAGON version 5.0) and an exhaustive search was performed in order to find the best regression equation with correlation coefficient (R) higher than 0.90 (STATISTICA version 6.0), finally the graphical representation of the calculated versus observed biological property is presented and eventually the prediction of new biologically active molecular structures. The newly proposed structures (S1-S8) show high biological activity values, S2 beeing the structure with the closest value of biological activity (log IC_{50}: 0.18) to the value shown by the reference structure (log IC_{50}: 0.176).

One of the widely used properties to describe the hydrophobicity/lipophilicity (partition coefficient of a compound between two immiscible phases) of a solvent is logP. These values were calculated using the program Chem Hyper: SR (-3.34); S2 (2.40); S3 (0.57). It

is known that a positive value of log P indicates the hydrophobicity of the molecule, which is very useful and important in the transport of biologically active substances through cell membrane. Summarizing this information the newly proposed structure, S2, seems promising in drug transport, therefore I think it would be interesting to synthesize this molecule to be subjected to tests of biological activity.

In chapter II, I investigated the structure and stability of two tetrapodal junctions: T_{j40} and T_{j52}. Geometry optimization and single point computations (total energy E_{tot} and HOMO-LUMO gap energy E_{gap}) were performed at the Hartree–Fock level of theory in view of evaluating their stability.

From the obtained data (Table II.3 and II.4) one can see that closed fullerenes show a higher strain in comparison to the open structures, the lowest value being for the IPR fullerene C_{60}, the reference structure in nanoscience. Observe the higher symmetry of the charged T_{j40}^{-4} resulted in higher strain, when compared with the neutral lower symmetry T_{j40}. Data from table II.3 sugests that the stability of the tetrapodal structure stability is close to that of C_{60}. The strain decreases in structures with more than one repeating unit (table II.4) while the HOMO-LUMO gap increases for the (hyper) cycles (Table II.4, entries 3 and 6), with T_{j40}-hexagon being the most stable structure in this table.

The next step was the theoretical study of the stability of simple and functionalized CNTs. From the obtained data we can conclude that functionalization of the nanotubes at one of the ends, leads to an increase of energy and therefore to an increase in their ability to react with different chemical compounds. Taken this fact into consideration, further reactions will have as starting structures functionalised CNTs at one of the ends. In further synthesis I obtained functionalized SWCNT, DWCNT and MWCNTs, with 1,3-diaminopropane, 1,6-diaminohexane, 1,7-diaminoheptane and 1,8-diaminooctane. The structures were characterized by elemental analysis, FT-IR spectroscopy and TEM microscopy, results showing that the functionalization took place in every case.

In chapter III, in order to study the capillarity of CNTs I used double sulphate of ammonium iron, lead nitrate and nickel nitrate solution. The amount of nitrogen present in the sample was followed through elemental analysis, and TEM images show the encapsulated metals in the inner cavity of the tubes. The best capacity of capillary can be attributed to MWCTs, because of their large internal diameter, and from the salts Fe shows the best capacity to enter into the cavity of CNTs, due to its smaller size.

Between the stiffness of theoretical formulations and the pragmatism of obtaining favorable solution must be a balance. Personal contributions made in this thesis were

subordinated to this principle, its goals being achieved and supported by the list of publications and participation in conferences.

LIST OF PUBLICATIONS

1. Tasnádi, E., Moldovan, C., Modeling the biological activity of 2-aryl-thiazole derivatives, *Studia Universitatis Babeş-Bolyai Chemia,* **2010**, 55, 4, 77-82
   IF = 0.231

2. Tasnádi, E., Katona, G., Diudea, M.V., Modeling of biologically active molecular structures, *Studia Universitatis Babeş-Bolyai Chemia*, **2010**, 55, 1, 45-54
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3. Füstös, M.E., Tasnádi, E., Katona, G., Diudea, M.V., Functionalization of carbon nanotubes, *Studia Universitatis Babeş-Bolyai Chemia*, **2010**, 55, 4, 153-159
   IF = 0.231

4. Nagy, K., Nagy, C.L., Tasnádi, E., Katona, G., Diudea, M.V., Hyper-diamonds and dodecahedral arhitectures by tetrapodal carbon nanotube junctions, *Acta Chemica Slovenica*, **2013**, 60, 1-4
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2. Tasnádi, E., Moldovan, C., Modeling the biological activity of 2-aryl-thiazole derivatives, *ICAM 7* (7th International Conference on Applied Mathematics) Mathematical Chemistry in NANO-era symposium, Cluj-Napoca, România, September 1 - 4, **2010**. (poster)

3. Tasnádi, E., Moldovan, C., Modeling the biological activity of 2-aryl-thiazole derivatives, *Workshop* organizat prin POSDRU Contract: POSDRU 6/1.5/S/3, Cluj-Napoca, România, 30 Septembrie **2010** (prezentare orală)

4. Tasnádi, E., Katona, G., Diudea, M.V., Studii corelationale pe set de benzodiazepine, *Workshop* organizat prin POSDRU Contract: POSDRU 6/1.5/S/3, Cluj-Napoca, România, 29 Septembrie **2009** (prezentare orală)

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